Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarket Adverse Event Review

Date:	December 13, 2012
Reviewer:	Vicky Huang, Pharm.D., BCPS, Safety Evaluator Division of Pharmacovigilance I
Team Leader:	Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader Division of Pharmacovigilance I
Medical Officer:	Ethan D. Hausman, M.D., Medical Officer Division of Pharmacovigilance II
Division Director:	Linda Scarazzini, RPh, MD, Director Division of Pharmacovigilance I
Product Name:	Intuniv® (Guanfacine hydrochloride, Extended-release)
Pediatric Labeling Approval Date:	February 25, 2011
Application Type/Number:	NDA #022037
Applicant/Sponsor:	Shire
OSE RCM #:	2012-1737

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA), the Division of Pharmacovigilance (DPV) was asked to summarize postmarketing reports of adverse events associated with the use of Intuniv® (guanfacine hydrochloride, extended-release) in pediatric patients (0-16 years of age). The main focus of this review is pediatric deaths and pediatric reports of serious unlabeled adverse events with Intuniv.

Intuniv (guanfacine hydrochloride, extended-release) is a selective alpha$_{2A}$-adrenergic receptor agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents ages 6 to 17 as monotherapy or as adjunctive therapy to stimulant medications.

The Adverse Event Reporting System (AERS) database was searched for all reports of adverse events (serious and non-serious) from October 1, 2010 through the "data lock" date of June 30, 2012. AERS contained 213 reports for Intuniv. Pediatric reports represent approximately 67% of the total (143/213).

In addition to reviewing serious pediatric reports (n=136), DPV also reviewed fatal reports with the age unknown (n=2) to determine if the report concerned a pediatric patient. One report with the age unknown included information to determine that the report described a pediatric patient; therefore, DPV identified 137 serious pediatric reports. After removing duplicates and excluded reports, DPV reviewed 124 pediatric cases reported with Intuniv.

DPV identified two fatal pediatric cases reported with the use of Intuniv in teenage males. One patient had a complicated psychiatric and social history who completed suicide by hanging. The cause of the second death was apparently accidental and was due acute poly-drug toxicity involving the combined effects of dextromethorphan and morphine.

Additionally, DPV identified 122 non-fatal serious cases; 64 cases reported unlabeled events and 58 cases reported labeled events. Half (n=32) of the cases of unlabeled events reported psychiatric adverse events, including 12 cases of hallucinations. The remaining 32 cases that reported unlabeled events reported nervous system adverse events (n=7), cardiac adverse events (n=6), gastrointestinal adverse events (n=5), and other miscellaneous adverse events (n=14). Forty-one (64%) of the cases of unlabeled adverse events were confounded by concomitant medications or concurrent disease states, provided insufficient information to make a causality assessment, or reported the persistence of events following treatment discontinuation of Intuniv.

Overall, the 58 cases that reported labeled adverse events are consistent with the current labeling.

Aside from the 12 cases of hallucinations, DPV did not identify any new safety concerns in the pediatric population.

DPV will conduct a FAERS search for hallucination-related adverse events reported with all formulations of guanfacine, across all ages, to assess whether this may be a safety concern. In addition, DPV will continue to monitor adverse events associated with the use of Intuniv.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Intuniv® (guanfacine hydrochloride, extended-release) received FDA approval on September 9, 2009 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents ages 6 to 17 as monotherapy or as adjunctive therapy to stimulant medications. See Appendix A for a summary of guanfacine formulations.

1.2 PEDIATRIC FILING HISTORY

First approval was on September 2009 for treatment of ADHD in patients 6 to 17 years. In February 2011, Intuniv was approved for adjunctive treatment with long-acting oral psychostimulants for the treatment of Attention Deficit Hyperactivity Disorder. In June 2011, the Overdose section of labeling was revised for consistency with current medical practice for treatment of guanfacine overdose.

A long-term maintenance study of safety and efficacy for monotherapy in patients 6 to 17 years old and an additional study to evaluate safety and efficacy in patients 13 to 17 years of age are planned; however, both studies have been deferred under PREA. Studies in children 0 to 5 years of age are waived because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.[1]

1.3 PEDIATRIC LABELING

Intuniv is currently approved for the use in children and adolescents 6 to 17 years; therefore, the entire label is relevant in the pediatric population.[2]

2 METHODS AND MATERIALS

2.1 AERS SEARCH STRATEGY

The Adverse Event Reporting System (AERS) was searched with the strategy described in Table 1. The FDA Adverse Event Reporting System (FAERS) was implemented after the search was conducted for this review. See Appendix B for a description of the FAERS database.

Table 1 AERS Search Strategy	
Date of search	July 25, 2012
Time period of search	October 1, 2010* through June 30, 2012
Product Names	Intuniv, guanfacine extended-release, and all associated active ingredients, trade and verbatim names
Other Product Criterion	NDA #022037
Search Parameters	Refer to Appendix C

* Previous OSE review reported adverse events through September 30, 2010

3 RESULTS

3.1 AERS REPORTS

Table 2. Total number of AERS reports* (October 1, 2010 through June 30, 2012)			
	All reports (US)[†]	Serious[‡] (US)	Death (US)
Adults (≥17 years)	7 (7)	6 (6)	0 (0)
Pediatrics (0-16 years)	143 (142)	136 (135)[§]	1 (1)[§]
Age unknown (null values)	63 (63)	60 (60)	2 (2)[§‖]
Total	213 (212)	202 (201)	3 (3)

* May include duplicates and have not been assessed for causality

[†] US counts in parentheses

‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

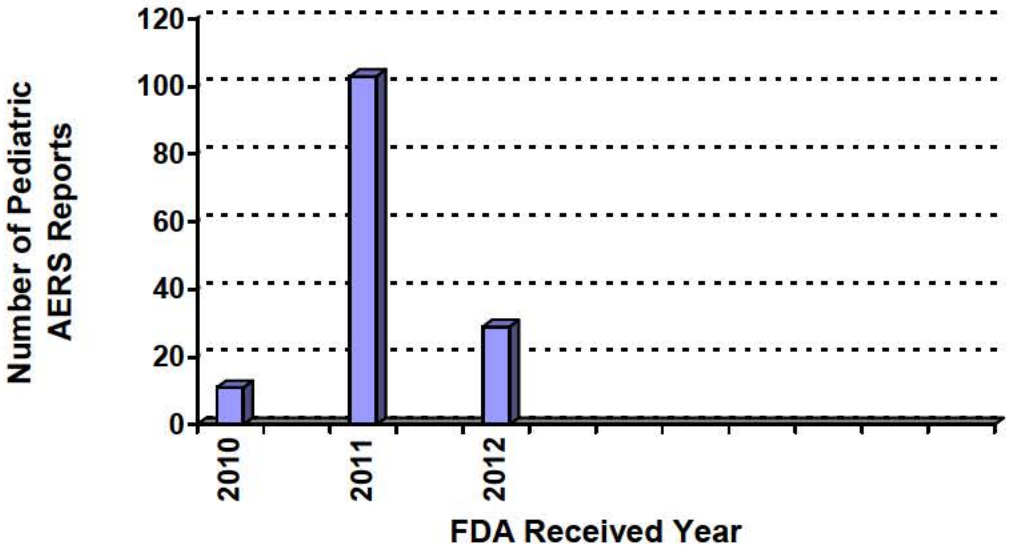
[§] See Figure 2

‖ One pediatric case identified.

3.2 TOTAL NUMBER OF PEDIATRIC REPORTS BY YEAR OF FDA RECEIPT (N=143)

These numbers for Intuniv include serious and non-serious reports, data only from reports where age (0-16 years) is known and may contain duplicate reports.

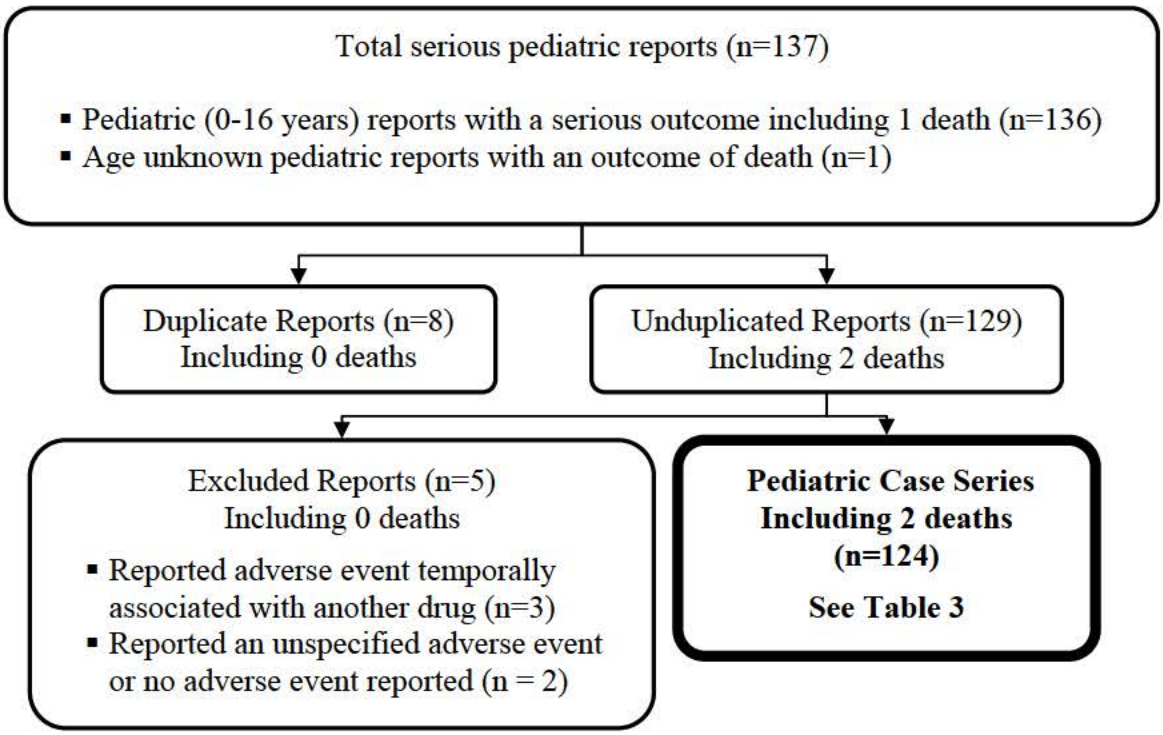
Figure 1. Total Number of Pediatric Reports (including serious and non-serious) for Intuniv, by year of FDA receipt (October 1, 2010 through June 30, 2012) (N=143)



3.3 SELECTION OF SERIOUS PEDIATRIC AERS CASES

DPV identified 136 pediatric reports with a serious outcome. In addition to reviewing pediatric reports with serious outcomes, DPV also reviewed all fatal reports with the age unknown to determine if the report concerned a pediatric patient. One fatal report with the age unknown included information to determine that the report described a pediatric patient; therefore, DPV identified 137 serious pediatric reports. **Figure 2** below summarizes the specific selection of cases reviewed in **Section 4**.

FIGURE 2: Selection of Serious Pediatric AERS Cases



3.4 DESCRIPTIVE CHARACTERISTICS FROM PEDIATRIC CASE SERIES

Table 3 summarizes the 124 AERS cases from the Pediatric Case Series with Intuniv.

Appendix C lists all the AERS case numbers, AERS ISR numbers and Manufacturer Control numbers for the Pediatric Case Series.

Table 3. Descriptive characteristics of Pediatric Case Series [October 1, 2010 through June 30, 2012]

(N=124)

Age	2-5 years	9
	6-11 years	86
	12-16 years	29
Sex	Male	78
	Female	40

	Unknown	6
Country of reporter	United States	123
	Foreign	1
Report type	Expedited	83
	Direct	24
	Periodic	17
Event date	2009	1
	2010	19
	2011	66
	2012	14
	Unknown	24
Primary Indications	ADHD	80
	Psychomotor Hyperactivity	3
	Autism	1
	Impulsive Behavior	1
	Unknown	39
Primary Serious Outcomes*	Death	2
	Hospitalized	31
	Life-threatening	5
	Disability	2
	Other serious	84

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

4 DISCUSSION OF SERIOUS PEDIATRIC CASE SERIES

4.1 SUMMARY OF PEDIATRIC DEATH CASES (N=2)

DPV identified two fatal cases reported with the use of Intuniv from October 1, 2010 through June 30, 2012. Attribution to guanfacine in both cases is not possible due to confounding medical issues or assignation of death to alternate causes (e.g. toxicity to alternate agents). Both cases are described below:

- Case Number 7388051, US: A 16-year-old male with an unknown medical history or concomitant medications was taking an unknown dose of Intuniv for an unspecified indication for an unspecified duration. He was found unresponsive on the bedroom floor of a private residence and pronounced dead at the scene. The medical examiner performed an autopsy and reported pulmonary congestion and edema as the only remarkable findings. His blood and urine were positive for morphine, dextromethorphan, nordextromethorphan, carisoprodol, meprobamate, and olanzapine; he was not tested for guanfacine. The medical examiner ruled the patient's death as an accident due to acute poly-drug toxicity involving the combined effects of dextromethorphan and morphine.
- Case Number 7886514, US: A 13-year-old male with a history of oppositional defiant disorder, affective disorder, reactive attachment disorder of infancy or early childhood, bipolar disorder (unconfirmed), "trouble at school," and

"girlfriend problems" was taking Intuniv 1 mg daily for ADHD without concomitant medications. Intuniv was titrated up to 4 mg daily in two months. Within one month of starting 4 mg daily, the clinical nurse specialist (CNS) reported the patient's pre-existing mood disorder worsened, described as "labile moods." As treatment, the CNS prescribed an unknown dose of fluoxetine, which was ineffective and discontinued after one month of use. The CNS then prescribed lamotrigine 25 mg daily and increased the dose to 75 mg twice daily; however, the event persisted. One month later, Intuniv was decreased to 2 mg daily and the event remained ongoing. Within one month of the dose change, he committed suicide by hanging himself. He was pronounced dead at the emergency room (ER).

4.2 SUMMARY OF UNLABELED PEDIATRIC ADVERSE EVENT CASES (N=64)

4.2.1 Psychiatric adverse events cases (n=32)

DPV identified 32 cases of unlabeled psychiatric adverse events reported with the use of Intuniv, including hallucinations (n=12), self-injurious ideation, suicide attempt, suicidal behavior, or suicidal ideation (n=12), aggression (n=3), homicidal ideation or physical assault (n=3), and other psychiatric adverse events (n=2), such as amnesia and somnambulism.

Hallucinations (n=12)

The cases were U.S. reports of males (n=8) and females (n=4) with a median age of 8 years old, ranging from 4 to 10 years old. The indications for Intuniv were ADHD (n=9), psychomotor hyperactivity and impulse control disorder (n=1), or unknown (n=2). The median daily dose of Intuniv was 2 mg, ranging from 1 mg to 3 mg (n=10). The median time to onset of event following initiating treatment with Intuniv was 10 days, ranging from 3 days to 5 months (n=7). The median duration of treatment with Intuniv was 15 days, ranging from 3 days to 6 months (n=7).

Eight cases reported abatement of symptoms with discontinuation of Intuniv; none of which reported re-exposure to Intuniv. Three of these eight cases were confounded by concomitant medications labeled for hallucinations (lisdexamfetamine, methylphenidate); two cases did not report the action taken on methylphenidate, and one case reported continued treatment with lisdexamfetamine. The fourth case was confounded by concurrent bipolar disorder. The fifth case reports concomitant use of risperidone without its indication; risperidone is indicated for schizophrenia (which may include hallucinations), bipolar mania, and irritability in children with autism. The remaining three cases did not report confounding factors but have incomplete clinical information; these three cases are summarized below:

- A 5-year-old female "became psychotic" and "seeing bugs and felt her bed was moving" three days after initiating treatment with Intuniv 1 mg (unknown frequency) for ADHD. Treatment with Intuniv discontinued after four days of use and the events resolved on the same day.

- An 8-year-old male experienced hallucinations within the same month of initiating treatment with an unknown dose of Intuniv for an unknown indication. He was not taking any concomitant medications. Treatment with Intuniv discontinued within the same month and the event resolved.
- A 10-year-old male was treated with an unknown dose of Intuniv for ADHD. On an unknown date, the patient started "hearing voices." Treatment with Intuniv discontinued on an unknown date and the event resolved.

Of the remaining four cases, three discontinued treatment with Intuniv, but did not report on the outcome of the event. The last case continued treatment with Intuniv and the event resolved.

Reviewer's comment: Like clonidine, guanfacine is a centrally acting alpha$_2$-adrenergic agonist used to treat pediatric patients with ADHD. Clonidine labeling is currently undergoing revision to uniformly describe occurrence of hallucinations in patients treated with the drug. DPV is performing a separate safety review to assess occurrence of hallucination in patients of all ages treated with guanfacine.

Self-injurious ideation, suicide attempt, suicidal behavior, or suicidal ideation (n=12)

The cases were U.S. reports of males (n=8) and females (n=4) with a median age of 9 years old, ranging from 6 to 16 years old. The indications for Intuniv were ADHD (n=6), hyperactivity (n=1), impulsive behavior (n=1), or unknown (n=4). The median daily dose of Intuniv was 2 mg, ranging from 1 mg to 26 mg (n=10). The median time to onset of event following initiating treatment with Intuniv was 8 days, ranging from 3 days to 10 months (n=7). Three cases reported the duration of treatment with Intuniv: 3 days, 2 weeks, and 1 month.

One case reported abatement of events after Intuniv use stopped and is summarized below:

- A 16-year-old male with ADD "took a number of pills" and "said he had no reason to live" after 2.5 days of treatment with Intuniv 1 mg daily. He was not taking a stimulant and had no previous incidents of suicide attempt or known thoughts of suicide. Treatment with Intuniv discontinued after 3 days of use and the event resolved. Five days after the event occurred, "he is in disbelief and can't resolve why he did this."

Of the remaining eleven cases, four were confounded by concomitant medications labeled for suicidal ideation (bupropion, cetirizine, levetiracetam, and sertraline), concurrent aggression, depression or obsessive-compulsive disorder (OCD), or a history of suicide attempt. Two of these four cases required hospitalization.

An additional two cases reported continued treatment with Intuniv; one case reported guanfacine dose reduction (from 2 mg to 1 mg), discontinued concomitant lisdexamfetamine and required treatment with paliperidone, and one case reported resolution of the event without a change in dose.

The remaining five cases provided insufficient clinical information to assess causality.

Reviewer's comment: Suicidality is not currently labeled. As discussed in a recent post-market safety review[3] and presentation to the Pediatric Advisory Committee[4], adolescents have an elevated risk of suicidality compared to the general population. A recent FDA epidemiology review[5] assessed the use of stimulant medication and atomoxetine in patients with ADD/ADHD and found no apparent increase risk for suicidality in patients treated with stimulants; however, there was a signal for suicidality with atomoxetine sufficient for labeling. DPV will continue to monitor for unconfounded cases of suicidality with Intuniv.

Aggression (n=3)

Two cases reported events abated after Intuniv use stopped; however, both cases were confounded by concomitant medications labeled for aggression (mixed amphetamine salts) or concurrent autistic spectrum disorder. The last case reported discontinued treatment with Intuniv, but did not report on the outcome of the event.

Reviewer's comment: DPV will continue routine monitoring.

Homicidal ideation / Physical Assault (n=3)

Assessment of all three cases is impaired by exposure to concomitant medicine, or pre-existing aggressive behavior, or inadequate clinical description. The two cases with clinical details are summarized below.

- An 8-year-old male who received Intuniv 2 mg four times daily for ADHD and an unspecified stimulant for an unknown indication experienced homicidal ideation after an undetermined period of treatment. Within the same month of the adverse event occurring, treatment with Intuniv discontinued and the event resolved. Additional clinical information was not available.

- A 6-year-old male with a history of severe aggression and foster care received Intuniv 2 mg at bedtime for ADHD and risperidone 0.5 mg three times daily for aggression. Within one month starting Intuniv, he experienced homicidal thoughts. His complete blood count, comprehensive metabolic panel, thyroid stimulating hormone level, and prolactin level were within normal limits. Intuniv was discontinued after one month of use and the event resolved within the same month.

Reviewer's comment: DPV will continue routine monitoring.

Other psychiatric adverse events cases (n=2)

A 13-year-old female experienced amnesia one month following initiating treatment with Intuniv 2 mg (unknown frequency) for ADHD. The event was described as "significant short term memory loss" and "failed" a physician-administered mini-mental status examination. Treatment with Intuniv discontinued and the event resolved within one week.

The last case reported somnambulism but lacked sufficient clinical information, to make an assessment.

Reviewer's comment: Spontaneous reports cannot be used to assess occurrence of common events due to drug exposure, and somnambulism is a common condition in the general population. DPV will continue routine monitoring.

4.2.2 Nervous system adverse events cases (n=7)

DPV identified seven cases of unlabeled nervous system adverse events reported with the use of Intuniv, including dysarthria or hypoesthesia (n=3), and other nervous system adverse events (n=4), such as benign intracranial hypertension, dyskinesia, parkinsonian rest tremor, and VIIth nerve paralysis. The cases were U.S. reports of males (n=5) and females (n=2) with a median age of 8 years old, ranging from 6 to 12 years old. The indications for Intuniv were ADHD (n=6) or unknown (n=1). The median daily dose of Intuniv was 3 mg, ranging from 2 mg to 4 mg. The median time to onset of event following initiating treatment with Intuniv was 3 weeks, ranging from 9 days to 5 months (n=5). The median duration of treatment for Intuniv was 5 months, ranging from 11 days to 6 months (n=4).

Dysarthria, Hypoesthesia (n=3)

Of the three cases, two reported that Intuniv use stopped on recognition of suspected adverse events; no case reported subsequent re-exposure to Intuniv with subsequent abatement of the events. These two cases are reporting abatement of symptoms are summarized below:

- A 6-year-old female experienced dysarthria described as "slurred her words" during the three weeks she received Intuniv 3 mg daily for ADHD. An unknown time after initiating treatment with Intuniv, she experienced a seizure. Treatment with Intuniv discontinued and the events resolved.
- A 7-year-old male with no significant medical history and no concomitant medications received Intuniv for ADHD. Nine days following initiating treatment with Intuniv 1 mg daily, he increased Intuniv to 2 mg, and experienced "lethargy, slurring of words, sleeping on and off, and numb cheeks." The next day, he was diagnosed with strep throat and started treatment with amoxicillin. He experienced a seizure the following day, described as "eyes rolled back in his head and he was shaking," and was taken to the ER. Treatment with Intuniv discontinued after 11 days and all events, except for the strep throat, resolved. Of note, both amoxicillin and Intuniv are labeled for convulsions.

The last case reported hypoesthesia and was confounded by concomitant medication already labeled for hypoesthesia (montelukast).

Reviewer's comment: While Intuniv is not labeled for dysarthria, is labeled for somnolence in Warnings and Precautions. DPV will continue routine monitoring.

Other nervous system adverse events cases (n=4)

The case of *benign intracranial hypertension* in a 10-year-old male, who was diagnosed with pseudotumor cerebri, reported the event resolved prior to treatment discontinuation with Intuniv after five months of use. The case of *dyskinesia* in a 12-year-old male reported the events of "uncontrolled body movements" as ongoing after treatment with Intuniv discontinued after almost six months of use. The case of *Parkinsonian rest tremor* in an 8-year-old male reported discontinued treatment with Intuniv within the same year as initiating treatment; however, the outcome of event was unknown. Reversible VIIth nerve palsy is most commonly due to infectious causes such as viruses or Lyme disease, and the case of *VIIth nerve palsy* in a 10-year-old female provided insufficient clinical information to assess causality.

Reviewer's comment: DPV will continue to monitor for these events.

4.2.3 Cardiac adverse events cases (n=6)

DPV identified six cases of cardiac adverse events reported with the use of Intuniv, including ventricular extrasystoles (n=3), heart rate increased (n=2), and electrocardiogram (EKG) QT prolonged (n=1). The cases were U.S. reports of males (n=4) and females (n=2) with a median age of 9 years old, ranging from 6 to 11 years old. The indications for Intuniv were ADHD (n=5) or unknown (n=1). The median daily dose of Intuniv was 3 mg, ranging from 2 mg to 4 mg. Two cases reported the time to onset of event following initiating treatment with Intuniv: same day and 4 months. One case reported treatment duration with Intuniv of 6 weeks.

Ventricular extrasystoles (n=3)

Of the three cases, one contained insufficient clinical information to assess, and one case confounded by concurrent Kawasaki's disease. The final case is detailed below:

- An 8-year-old male without significant medical history or concomitant medications received Intuniv for ADHD. He initiated treatment with Intuniv 1 mg daily then titrated up to 4 mg daily on an unknown date. While on Intuniv 4 mg, he experienced "heart skipping beats," which was diagnosed as ventricular tachycardia at the ER. At the ER, he also experienced bradycardia (heart rate not reported). On an unknown date, a complete work-up by the cardiologist revealed AV block of an unknown degree, *however a Holter monitor revealed no abnormalities*. Within the same month of the ER visit, Intuniv dose decreased to 3 mg daily and all events resolved in the same month.

Heart rate increased (n=2)

Two cases of heart rate increased in 6- and 10-year-old females who received Intuniv for ADHD. One case reported continued treatment with Intuniv and the events were resolving at the time of report. The second case provided insufficient information, such as action taken on Intuniv or the outcome of events, to make a causality assessment.

EKG QT prolonged (n=1)

An 11-year-old male with Asperger syndrome and bipolar disorder received Intuniv 3 mg every morning for ADHD and aripiprazole 10 mg at bedtime. An unknown time following initiating treatment with Intuniv, he experienced lightheadedness and heart rate in the "40s." He was diagnosed with bronchopneumonia and was "strep B positive," and treated with intravenous antibiotics and albuterol. His EKG was suspicious for prolonged QT syndrome (results not reported) the next day. Five days later, he presented to the ER with dizziness, lightheadedness, heart rate in the "30s," and his EKG showed sinus bradycardia with QTc 375 (prolonged QT resolved). Treatment with Intuniv discontinued after 6 weeks of use. Causality assessment is uninterpretable due to concomitant exposure to unspecified intravenous antibiotics, lack of reported QT on presentation, and a documented normal QTc without relationship to discontinuation of medication.

Reviewer's comment: The AERS data yielded no reliable cardiac signal and DPV will continue routine monitoring.

4.2.4 Gastrointestinal adverse events cases (n=5)

DPV identified five cases of gastrointestinal adverse events reported with the use of Intuniv, including pancreatitis (n=3), gastric hemorrhage (n=1), and hepatic enzyme increased (n=1). The cases were U.S. reports of males (n=4) and females (n=1) with a median age of 8 years old, ranging from 4 to 13 years old. The indications for Intuniv were ADHD (n=2) or unknown (n=3). Three cases reported the daily dose of Intuniv: 1 mg, 2 mg, and 3 mg. Two cases reported the time to onset of event following initiating treatment with Intuniv: 2 months and 1 year. One case reported treatment duration with Intuniv of one year.

Pancreatitis (n=3)

The first case is a 4-year-old male with "severe" ADHD initially received treatment with "regular" guanfacine and no concomitant medications. Six months later, his treatment changed to Intuniv, which was titrated from 1 mg to 3 mg over 8 months. Four months after starting Intuniv 3 mg, he experienced abdominal pain and vomiting, which prevented him from taking Intuniv; thus, Intuniv discontinued without a taper. He then experienced respiratory arrest, seizure and rebound hypertension, and was admitted to the hospital with pancreatitis [(lipase was >10,000 and amylase was 1680 (no units provided)]. He was evaluated by a nephrologist and a gastroenterologist, and treated with clonidine as needed for rebound hypertension. He had no history of trauma, cardiac and renal etiologies were negative, and no other etiology found. His lipase and amylase returned to normal levels several days after hospitalization.

The second case is an 8-year-old male who received Intuniv for an unknown indication. His past and concurrent medical history or concomitant medications were not reported. Two months after starting Intuniv, he was hospitalized for symptoms of food poisoning, and was later diagnosed with pancreatitis, thrombocytosis ("close to 1 million platelets") and a colonoscopy revealed "inflamed/infectious." Treatment, action taken on Intuniv and outcome of events are unknown.

The third case is a 13-year-old female who received Intuniv for an unknown indication. She was not taking any concomitant medications, but her past and concurrent medical histories were not reported. On an unknown date, she developed acute pancreatitis and was hospitalized. Treatment while hospitalized was not reported. Treatment with Intuniv discontinued on an unknown date and the event resolved on an unknown date. The temporal relationship between the onset and the resolution of event with the initiation and discontinuation of Intuniv cannot be established.

Reviewer comment: For the first case, despite resolution of pancreatitis after discontinuation of guanfacine, and the statement that no other etiology was identified, it is not possible to conclude the event was caused by guanfacine. The second and third cases contain insufficient clinical information to link Intuniv to pancreatitis. DPV will continue monitor for reports of pancreatitis.

Other gastrointestinal adverse events cases (n=2)

An 8-year-old male with no significant medical history received Intuniv 2 mg daily for an unknown indication. He was not receiving concomitant medications. An unknown time after initiating treatment with Intuniv, he was hospitalized for gastritis and gastric bleeding. Upon admission, his hemoglobin levels were 11.1 and 9.8 (no units provided). As treatment, he received a blood transfusion and discontinued Intuniv. The events resolved 4 days later.

The case of hepatic enzyme increased provided insufficient information to make causality assessments.

Reviewer comment: DPV will continue to monitor for these events.

4.2.5 Other unlabeled adverse events cases (n=14)

The remaining 14 unlabeled adverse events not categorized in the above sections are summarized in Appendix E. Based on the limited number of reports received for each of these events and limited clinical information in these reports, no conclusions can be made regarding an association between the reported event and Intuniv.

4.3 SUMMARY OF LABELED PEDIATRIC ADVERSE EVENTS CASES (N=58)

DPV identified 58 cases with labeled adverse events. Thirty-five cases reported nervous system adverse events, such as syncope (n=19), convulsion (n=11), somnolence (n=4) and headache (n=1). Eight of the 11 convulsion cases were confounded by concomitant medications labeled for convulsions (e.g., divalproex sodium, felbamate, lamotrigine, lisdexamfetamine, methylphenidate, mixed amphetamine salts, risperidone), a report of concomitant unspecified anti-seizure medication, or a past medical history of staring spells and febrile seizure. The remaining three cases of convulsion provided insufficient information to make causality assessments.

Seventeen cases reported cardiac adverse events, such as bradycardia (n=10), hypotension (n=4), atrioventricular block (n=2), and chest pain (n=1). The first case of

atrioventricular block reported resolution of symptoms following discontinuation of Intuniv and unspecified treatment during hospitalization, without re-exposure to Intuniv. In the second case of atrioventricular block, a cardiologist re-read the EKG and determined it was "normal without 1st degree AV block."

The remaining six cases reported four psychiatric adverse events (e.g., anxiety, depression, fatigue, lethargy), and two miscellaneous adverse events (e.g., abdominal pain upper, enuresis).

Table 4 summarizes these labeled adverse events and the sections of the Intuniv label where they are located.

Table 4. Labeled Adverse Events in the Intuniv label

Adverse Event	*Warnings & Precautions*	*Adverse Reactions*	*Drug Interactions*	*Overdosage*
Cardiac				
Bradycardia	√	√	√	√
Hypotension	√	√	√	√
Atrioventricular block		√		
Chest pain		√		
Nervous System				
Somnolence	√	√	√	√
Syncope	√	√	√	
Convulsion		√		
Headache		√		
Psychiatric				
Lethargy		√		√
Anxiety		√		
Depression		√		
Fatigue		√		
Miscellaneous				
Abdominal pain upper		√		
Enuresis		√		

5 CONCLUSION

DPV reviewed 124 serious pediatric cases reported with Intuniv use. There were two fatal pediatric cases in teenage males in our case series. One patient had a complicated psychiatric and social history who completed suicide by hanging. The cause of the second death was apparently accidental and was due acute poly-drug toxicity involving the combined effects of dextromethorphan and morphine.

DPV identified 122 non-fatal serious cases; 64 cases reported unlabeled events and 58 cases reported labeled events. Half (n=32) of the cases of unlabeled events reported psychiatric adverse events. Twelve of the 32 cases of psychiatric adverse events reported hallucinations. The remaining 32 cases that reported unlabeled events reported nervous

system adverse events (n=7), cardiac adverse events (n=6), gastrointestinal adverse events (n=5), and other miscellaneous adverse events (n=14). Forty-one (64%) of the cases of unlabeled adverse events were confounded by concomitant medications or concurrent disease states, provided insufficient information to make a causality assessment, or reported the persistence of events following treatment discontinuation of Intuniv.

Overall, the 58 cases that reported labeled adverse events are consistent with the current labeling.

Aside from the 12 cases of hallucinations, DPV did not identify any new safety concerns in the pediatric population.

6 RECOMMENDATIONS

DPV will conduct a FAERS search for hallucination-related adverse events reported with all formulations of guanfacine, across all ages, to assess whether this may be a safety concern. In addition, DPV will continue to monitor adverse events associated with the use of Intuniv.

7 REFERENCES

1. Intuniv Approval Letter, September 2009.
2. Intuniv [package insert]. Wayne, PA: Shire Pharmaceuticals Inc; 2011.
3. Huang V. Vyvanse Pediatric Postmarket Adverse Event Review. June 14, 2012.
4. Hejazi N. Pediatric focused safety review: Vyvanse® (lisdexamfetamine dimesylate) Pediatric Advisory Committee Meeting. September 11, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM319371.pdf
5. Mosholder A. Psychiatric adverse events in clinical trials of drugs for Attention Deficit Hyperactivity Disorder (ADHD). March 3, 2006.
6. Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. (Accessed September 25, 2012)

8 APPENDICES

8.1 APPENDIX A. SUMMARY OF GUANFACINE FORMULATIONS[6]

Brand Name	Formulation	NDA Number	Indication	FDA Approval Date
Intuniv®	Tablet, Extended release; Oral	022037	ADHD for patients aged 6 – 17 years old	September 2, 2009
Tenex®	Tablet; Oral	019032	Hypertension	October 27, 1986

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. AERS STANDARD SEARCHES

A. Adults (17 yrs and above)
   1. All outcomes from approval date (no set criteria)
   2. Serious outcomes from approval date
   3. Death as an outcome from approval date

B. Ages 0-16 yrs ONLY
   1. Same as above 1-3

8.4 Appendix D. AERS Case Numbers (CSENUM), AERS ISR Numbers (ISRNUM) and Manufacturer Control Numbers (MFRCNTRL)

CSENUM	ISRNUM	MFRCNTRL
7388051	7056801	US-SHIRE-SPV1-2010-00908
7616917	7027758	US-SHIRE-SPV1-2010-01683
7667630	7101202	US-SHIRE-SPV1-2010-01957
7669979	7104725	US-SHIRE-SPV1-2010-01965
7672469	7108096	US-SHIRE-SPV1-2010-01971
7673663	7322562	US-SHIRE-SPV1-2010-01978
7689447	7151495	US-SHIRE-SPV1-2010-02054
7692537	7136552	US-SHIRE-SPV1-2010-02078
7702693	7245267	US-SHIRE-SPV1-2010-02117
7723793	7124666	CTU 436411
7723976	7127826	SPV1-2010-01201
7723995	7127829	SPV1-2010-01502
7759905	7225387	US-SHIRE-SPV1-2011-00043
7807172	7285403	US-SHIRE-SPV1-2011-00208
7825510	7497169	US-SHIRE-SPV1-2011-00284
7826869	7464527	US-SHIRE-SPV1-2011-00303
7828839	7292939	CTU 443923
7831109	7517175	US-SHIRE-SPV1-2011-00327
7831157	7293138	CTU 444001
7855722	7328544	CTU 445688
7883393	7638733	US-SHIRE-SPV1-2011-00522
7886514	7395992	US-SHIRE-SPV1-2011-00558
7889553	7371381	CTU 448250
7891963	7403949	US-SHIRE-SPV1-2011-00098
7901883	7419606	US-SHIRE-SPV1-2011-00611
7902130	7419977	US-SHIRE-SPV1-2011-00631
7916090	7439257	US-SHIRE-SPV1-2011-00667
7918811	7419784	CTU 450624
7919856	7444489	US-SHIRE-SPV1-2011-00648
7920364	7445196	US-SHIRE-SPV1-2011-00668
7928858	7557512	US-SHIRE-SPV1-2011-00707
7944072	7457384	CTU 452311
7947451	7570975	US-SHIRE-SPV1-2011-00783
7953758	7803951	US-SHIRE-ALL1-2011-01487
7960376	7635829	US-SHIRE-SPV1-2011-00833
7962323	7506354	US-SHIRE-SPV1-2011-00827
7974911	7501795	CTU 454356
7975272	7496606	CTU 454228
7983660	7649022	US-SHIRE-ALL1-2011-01693
7983661	7536958	US-SHIRE-ALL1-2011-

CSENUM	ISRNUM	MFRCNTRL
		01700
7986430	7540906	US-SHIRE-ALL1-2011-01733
7991203	7547987	US-SHIRE-ALL1-2011-01806
7991236	7516792	SPV1-2010-02236
7991241	7516793	SPV1-2011-00043
7991249	7516824	SPV1-2011-00191
7991252	7516826	SPV1-2011-00208
8010680	7574145	US-SHIRE-ALL1-2011-01882
8012711	7562221	CTU 457081
8017983	7585276	US-SHIRE-ALL1-2011-02049
8027921	7670777	US-SHIRE-ALL1-2011-02070
8032832	7606165	US-SHIRE-ALL1-2011-02138
8035961	7600283	SPV1-2011-00419
8035963	7600302	SPV1-2011-00454
8035964	7897135	SPV1-2011-00634
8036172	7610276	US-SHIRE-ALL1-2011-02143
8036408	7610517	US-SHIRE-ALL1-2011-02131
8036982	7600234	ALL1-2010-02240
8037001	7897212	ALL1-2011-01622
8044552	7725318	US-SHIRE-ALL1-2011-02227
8063085	7647728	US-FDA-7647728
8064601	7650052	US-FDA-7650052
8070403	7658067	US-SHIRE-SPV1-2011-00802
8084099	7674373	US-SHIRE-ALL1-2011-02600
8090032	7763752	US-SHIRE-ALL1-2011-02702
8126125	7736821	US-FDA-7736821
8133156	7746394	US-FDA-7746394
8157391	7779764	US-SHIRE-ALL1-2011-03555
8161096	7892350	US-SHIRE-ALL1-2011-03594
8184268	7818293	US-SHIRE-ALL1-2011-03952
8185935	7820255	US-SHIRE-ALL1-2011-

CSENUM	ISRNUM	MFRCNTRL
		03759
8195624	7833990	US-SHIRE-ALL1-2011-03992
8198862	8017541	US-SHIRE-ALL1-2011-04057
8198864	7844303	US-SHIRE-ALL1-2011-04058
8200414	7852048	US-SHIRE-ALL1-2011-04114
8203374	8474745	US-SHIRE-ALL1-2011-04037
8217077	7878587	US-FDA-7878587
8220791	7883243	US-SHIRE-ALL1-2011-04211
8220792	7883244	US-SHIRE-ALL1-2011-04225
8236366	7897111	ALL1-2011-02874
8239197	7906426	US-SHIRE-ALL1-2011-04333
8239319	7897221	ALL1-2011-01717
8239321	7897257	ALL1-2011-01718
8239330	7897279	ALL1-2011-02131
8239342	7897287	ALL1-2011-02208
8241619	7910019	US-SHIRE-ALL1-2011-04387
8242440	7911267	US-SHIRE-ALL1-2011-04353
8242623	7897302	ALL1-2011-02267
8242959	7906316	CTU 465393
8248080	7919227	US-SHIRE-ALL1-2011-04422
8248900	7920659	US-SHIRE-ALL1-2011-04441
8257515	7931576	US-FDA-7931576
8261415	7937087	US-SHIRE-ALL1-2011-04547
8264236	7941660	US-FDA-7941660
8264257	7941682	US-FDA-7941682
8270757	7951938	US-SHIRE-ALL1-2011-04653
8270759	7951941	US-SHIRE-ALL1-2011-04489
8286036	7973558	US-SHIRE-ALL1-2011-04728
8290550	7978998	US-SHIRE-ALL1-2011-04905
8297619	8158845	US-SHIRE-ALL1-2011-04909
8341376	8052583	US-SHIRE-ALL1-2012-00212
8341377	8182605	US-SHIRE-ALL1-2012-00183
8347911	8061808	US-SHIRE-ALL1-2012-00251
8351793	8067352	US-SHIRE-ALL1-2012-00306
8381702	8286648	US-SHIRE-ALL1-2012-00458
8384275	8271471	US-SHIRE-ALL1-2012-00548
8393692	8118962	US-SHIRE-ALL1-2012-00631
8401854	8130832	US-SHIRE-ALL1-2012-00742
8416650	8150396	US-SHIRE-ALL1-2012-00912
8424798	8282430	US-SHIRE-ALL1-2012-01061
8424799	8162695	US-SHIRE-ALL1-2012-00983
8462419	8214119	US-SHIRE-ALL1-2012-01413
8462420	8319099	US-SHIRE-SPV1-2012-00249
8467771	8221745	US-FDA-8221745
8471107	8226816	US-SHIRE-ALL1-2012-01469
8481845	8242953	US-FDA-8242953
8510236	8282341	US-SHIRE-ALL1-2012-00874
8513580	8286650	US-SHIRE-ALL1-2012-01867
8525508	8304289	US-FDA-8304289
8535525	8320505	US-FDA-8320505
8546001	8464585	US-SHIRE-ALL1-2012-02112
8580567	8381938	CTU 475990
8582174	8389407	US-SHIRE-ALL1-2012-02621
8619082	8444131	US-SHIRE-ALL1-2012-02807
8629479	8457823	US-SHIRE-ALL1-2012-02997

8.5 APPENDIX E. SUMMARY OF OTHER UNLABELED ADVERSE EVENTS CASES (N=14)

Unlabeled Adverse Event	N	Summary / Comments
Lip swelling	2	A 9-year-old female received Intuniv 2 mg daily for an unknown indication. Subsequently, she experienced swelling of lips and lips "drooped" that required an ER visit. She was treated with epinephrine and prednisone, and the events resolved. Treatment with Intuniv discontinued. A 13-year-old female initiated treatment with Intuniv 1 mg daily for ADHD two months after initiating treatment with doxycyline for acne. Two months following initiating treatment with Intuniv and dose titrations, "a small amount of blood was found on the patient's pillow and the patient coughed up a little bit of blood... experienced swelling of her bottom lip." Hemoptysis resolved, the orthodontist saw no evidence of gum or mouth bleeding. Treatment with Intuniv and doxycycline continued and lip swelling persisted.
Eye and face swelling, rash erythematous	1	A 14-year-old male received Intuniv 1 mg (unknown frequency) and methylphenidate transdermal system 20 mg daily. Subsequently, he experienced "swollen eyes, swollen face, fine red rash on face... pale... lethargic/groggy... incoherent speech." No additional clinical information provided.
Abnormal loss of weight	1	A 7-year-old female with a history of asthma, autism, and constipation received treatment with albuterol, aripiprazole, fluticasone/salmeterol inhaler, lisdexamfetamine (since 2008), and polyethylene glycol 3350. Within the same month of starting Intuniv 1 mg, she experienced an unintentional weight loss of 7 pounds in 1 month, and weighing 55 pounds at the time of report. Treatment with all medications continued and the event remained ongoing.
Blindness transient	1	An 11-year-old female with ADHD, Tourette's disorder and Von Willebrand's disease received mixed amphetamine salts and Intuniv. Eleven days after staring Intuniv or four days after Intuniv increased to 2 mg daily, she experienced transient blindness, described as "saw blackness," weakness and loss of coordination. Treatments at the ER included water, acetaminophen, and discontinued Intuniv; however, the events remained ongoing.
Blood potassium decreased	1	A 12-year-old male with ADHD experienced lightheadedness, fainted, and incontinent of urine during the first week of starting Intuniv 2 mg daily. His vital signs at the ER were within normal limits, but his serum potassium was reported as "low" (values not provided). Treatment with Intuniv discontinued. All events except low serum potassium resolved.
Dyspnea, oropharyngeal pain	1	An 8-year-old male experienced chest pain, trouble breathing, neck and throat pain 4 days following initiating treatment with an unknown dose of Intuniv for an unknown indication. Action taken on Intuniv and the outcome of the events were unknown.
Epistaxis	1	A 12-year-old male experienced 2 episodes of "blacking out" while at school, 4 episodes of epistaxis, described as "significant nosebleeds," 1 month following initiating treatment with Intuniv 2 mg daily for ADHD. Treatment with Intuniv continued, but the outcome of events was unknown.
Hemorrhagic diathesis	1	An 11-year-old male with a history of hemophilia received Intuniv 2 mg daily and dexmethylphenidate 15

		mg daily for ADHD. One month following initiating treatment with Intuniv, he experienced increased bleeding episodes. Treatment with Intuniv discontinued after almost two months of use, but the outcome of the event was unknown.
Hematoma	1	A 7-year-old of unknown sex received an unknown dose of Intuniv for ADHD. On an unknown date, he passed out and was taken to the ER. Additionally, he developed a hematoma. Subsequently, treatment with Intuniv discontinued. Loss of consciousness resolved, but the outcome of hematoma was unknown.
Henoch-Schonlein Purpura	1	A 7-year-old male received Intuniv 1 mg daily for ADHD without concomitant medications. Eight days following initiating treatment with Intuniv, he developed a rash and was hospitalized. He was diagnosed with Henoch-Schonlein Purpura. Treatment with Intuniv discontinued after less than one month of use, but the event remained ongoing.
Neutropenia	1	An 8-year-old male received an unknown dose of Intuniv along with several unspecified medications for unknown indications. On an unknown date, he experienced neutropenia (values not reported), low blood pressure, and dizziness. Subsequently, he was hospitalized. Treatment with Intuniv discontinued and neutropenia resolved as his white blood cell count returned to normal (values not reported).
Pharyngitis streptococcal	1	A 9-year-old female with no significant medical history received Intuniv 3 mg daily and methylphenidate transdermal system for ADHD. Subsequently, he experienced a "strep throat." Treatment with Intuniv discontinued, but the outcome of the event was unknown.
Tinnitus	1	A 13-year-old male experienced tinnitus during treatment with Intuniv for ADHD. He initiated treatment with Intuniv 1 mg daily and increased to 2 mg daily over 15 days. Treatment with Intuniv discontinued after 15 days of use and the event resolved.